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10/692,918	10/24/2003	Frank Grosveld	CARP0015-101	9062

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,918	GROSVELD, FRANK	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,10,11,33,39,41,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7, 10-11, 33, 39, 41, 43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims filed October 16, 2009 has been received and entered. Applicants have canceled claims 2-6, 8-9, 12-32, 34-38, 40 and 42. Claims 1, 7, 10-11, 33, 39, 41, 43 and 44 are pending in this application.

Election/Restrictions

Applicant's election with traverse of group I in the response filed dated April 27, 2006 was acknowledged. The traversal was on the grounds that Group I and Group II-III should be examined together because search for invention of Group I would be coextensive with Group II and III. In addition, applicants asserted that only method of Group I would be required to make the antibody recited in Groups II and III. Applicant's arguments for examining elected method group with the product claims were not persuasive for the reasons of record (see office action dated 2/12/2007). Therefore, the requirement for restriction was deemed proper, maintained and made FINAL. Claims 1, 7, 10-11, 33, 39, 41, 43 and 44 are under consideration.

Priority

It is noted that applicants have previously relied on the post filing art of Janessens et al (Proc. National Academy of Science, 2006, 15130-15130, art o record) for the enabling support of instant application that is a continuation (CON) of PCT/IB02/02303 filed on 04/24/2002 which claims benefit from application GB0110029.6 filed in Great Britain on 4/24/2001. It is in this context, while comparing the method disclosed in different application with the post filing art presented by applicants, Examiner noted that claims are not enabling to produce single heavy chain antibody in a transgenic nonhuman mammal disclosed in provisional application filed in GB. However, applicants' arguments that claimed method does not require loxP site and US Patent 10/29/1996 describes the isotope switching using switch regions is persuasive. Therefore, the effective filing date for instant claims 1, 7, 10-11, 33-36, 39, 41, 43 and 44 is 04/24/2001.

Withdrawn- Claim Rejections -35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7, 10-11, 33, 39, 43 and 44 were rejected under 35 U.S.C. 112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention. Applicants arguments filed October 16, 2009 have been fully considered and found persuasive. Applicant arguments filed October 16, 2009 in conjunction with the Weiner, Grosschedl and Grosveld declaration filed on 2/7/2008 is persuasive. Therefore previous rejection of record is hereby withdrawn.

The previous office action indicated an enabled scope for a method for the production of a single heavy chain antibody in a transgenic mouse comprising expressing a heterologous VHH heavy chain locus in said mouse specifically in B cells in response to antigen challenge, wherein the VHH heavy chain locus is integrated into the mouse genome and said VHH heavy chain locus comprises in germ-line configuration: (a) at least one VHH exon, at least one-D exon and at least one-J exon, wherein the VHH exon, the D exon and the J exon are capable of recombining to form VDJ coding sequence, and wherein the VHH exon comprises a naturally occurring llama VHH coding sequence, and (b) a constant heavy chain region comprising at least one C constant heavy chain gene and at least one of Cγ, Cα, Cε, or Cδ constant heavy chain gene, wherein each of said at least one constant heavy chain gene, when expressed, does not express a functional CH1 domain, (c) a regulatory sequence providing for expression of the VHH heavy chain locus specifically in B cells, said method comprising: 1) immunizing said mammal with an antigen and 2) isolating single heavy chain antibody against said antigen from said mouse, does not reasonably provide enablement for a method for producing single chain antibody in any other nonhuman mammal. The previous rejection for not reasonably providing enablement for a method for producing single chain antibody in other nonhuman mammal is withdrawn. In the instant case, applicants' arguments that claim are fully enabling for the

breadth of the claims is found persuasive because of following arguments and evidence on record during the prosecution of this application.

(i) introduction of transgene into the germline of non-human mammalian systems was well established at the time of filing.

(ii) regulatory elements that ensure high levels of B-cell specific IgH were well characterized and were known to be present in the human IgH genomic sequence described, moreover these were known to be functional when incorporated in transgene in non-human mammals at the time of filing.

(iii) at the time of filing, there was a wealth of evidence to demonstrate that enhancer and LCR elements derived from one mammalian species (including human) are functional in other mammalian species.

(iv) the endogenous locus should not interfere with trangene expression because allelic exclusion will ensure that some cells will express only the transgene across different species (see arguments filed on 9/29/2008, page 15 and 16 and 10/16/2009 (page 7) and the Weiner declaration, paragraph 20 and 21).

(v) the assembly of complex heavy chain immunoglobulin loci as functional transgenes was well established in the art prior to the filing date (see argument filed 9/29/08, page 17).

(vi) naturally occurring VHH loci were known at the time of filing, and any such locus would work (see pages 8 and 9 the argument filed 06/02/09 and 10/16/2009, page 8).

Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot.

Withdrawn-Claim Rejections - 35 USC § 112

Claim34-36 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' cancellation of claims 34-36 renders their rejections moot.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 7, 10-11, 39, 41, 43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Surani et al (US Patent no 5545807, dated 8/13/1996), Lonberg et al (US Patent no 5625126, dated 4/29/1997, art of record), Nguyen et al (Molecular Immunology, 1999, 515-524) and NCBI accession no. (AF305944, dated 3/15/2001).

With respect to claim 1, 7, 10-11, 39, 41, 43, Surani et al teach a method to produce an antibody in a transgenic mouse comprising a heterologous chimeric construct that generate antibody specifically in B cell of said mouse in response to antigen challenge, wherein the hybrid unrearranged immunoglobulin heavy chain gene comprising a mouse VH gene segment, a human VH gene segment, human and mouse D gene segments, human J gene segments, and a gene segment encoding a human mu constant effector region (see col. 3, lime 7-16 and col. 4, line 9-47). It is noted that Surani et al also teach that the vector also contains the necessary IgH enhancer required for B-cell specific expression (see col. 14, line 37). Surani et al teach immunizing said mouse to establish hybridoma which produced antibodies comprising human heavy chain and mouse light chain (example 3 and claim 5 of '807). While, Bruggemann and teach that hybrid loci comprising different element from different species are functional, but differ from claimed invention by not explicitly teaching construct generating antibody of different isotype by class switching.

However, such was known in prior art. For instance, Lonberg et al ('126) teach a method to induce heterologous antibody production of various isotypes, including: IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgA, IgD, of IgE (col. 4, line 9-10) in the transgenic mouse (col. 2, lines 59-60). It is noted that the method involves undergoing isotype switching that occurs by recombination events which involve at least one switch sequence region in the transgene (col. 4, lines 34-40). Furthermore, the recombination of variable region gene segments to form functional heavy and light chain variable regions is mediated by recombination signal sequences (RSS's) that flank recombinationally competent V, D and J segments. Lonberg disclose that these sequences are found on the J, or downstream side, of each V and D gene segment (col. 22, lines 22-45). Lonberg also disclose mice that produce B cells is also capable of alternatively expressing antibodies comprising fully human heavy chains and antibodies comprising chimeric (human variable/mouse constant) heavy chains, by trans-switching (col. 43, lines 3-45). Lonberg discloses that the immunoglobulin heavy chain transgene could comprise one or more of each of the VH, D, and JH gene segments and two or more of the CH genes. It is noted that with regard to the CH segments for the heavy chain transgene, it is preferred that the transgene contain at least one μgene segment and at least one other constant region gene segment, more preferably a γ gene segment. Lonberg discloses that switch regions can be linked upstream heavy chain C gene

that do not naturally occurs next to a particular switch region (col. 33, lines 1-6). It is also noted that Lonberg contemplate a C2 segments that is preferably a human γ1 or γ 3 genes. Lonberg also discloses that murine γ2a and γ2b can also be used, as many downstream (i.e., switched) isotype genes form various other species (col. 34, lines 19-24). Lonberg teaches that the switch regions used in the transgene are preferably murine or human (col. 33, lines 62-67). In addition, Lonberg also discloses a vector pGP1h that includes the promoter leader sequence exon (example 18). However, Lonberg et al (126') do not disclose a transgene wherein VH region comprises a naturally occurring VHH region that produces a single chain heavy antibody devoid of light chain.

The deficiency of Surani et al and Loneberg is cured by Nguyen who teaches that heavy-chain antibodies (HCAbs) lack the segments first domain of the constant region (CH1), which is present in the genome but is spliced. It is disclosed that loss of the splice consensus signal is responsible for the removal of the entire CH1 domain in camel g2a heavy-chain Immunoglobulins (see abstract). Nguyen et al also teach complete nucleotide (nt.) sequence of the camel g2a heavy-chain constant gene obtained from a liver genomic library (see, page 516, col. 2, para. 2). NCBI accession no provided the germ-line VHH coding sequence.

Thus, based upon the need to enlarge the primary Ag-binding repertoire of the HCAb using a VHH coding sequence taught by NCBI accession no and in view of detailed guidance provided in the Loneberg and Surani et al specification for switch sequence, constant region sequence, cloning methodology and method for generating heterologous antibody in a mouse for generating heterologous antibody in a mouse, it would have been *prima facie* obvious to the skilled artisan to modify the method of Surani et al by substituting the VH gene segment with a VHH exon comprising naturally occurring VHH coding sequence disclosed by Nguyen et al/NCBI accession number with reasonable expectation of success. A person of skill in the art would have been motivated to substitute human or mouse VH gene segment disclosed by Surani et al with VHH coding sequence disclosed by NCBI accession, as a matter of design choice, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One of ordinary skill in the art would have been motivated to produce heterologous antibody in a mouse by further optimizing and changing constant heavy chain gene from other species such as mouse and rabbit. Lonberg had already disclosed that switch region from different isotype can be operatively linked to a particular constant region, the skilled artisan would have been motivated to use either a switch region of same isotype or a switch region of different isotype to promote class switch to any particular constant region gene. Thus in view of detailed teaching of Lonberg as discusses above, it would have been *prima facie* obvious to the skilled artisan at the time of filing to modify the switch region of different species as taught by Lonberg. Furthermore, Nguyen et al had already described that heavy-chain antibodies (HCAbs) lack the segments of first domain of the constant region (CH1), thus one of ordinary skill would be motivated to splice CH1 domain such that constant heavy chain gene when expressed does not express a functional CH1 domain to produce only single heavy chain antibody devoid of light chains. One of ordinary skill in the art would be motivated to do so as it was known in the art that single chain heavy antibody recognizes broad range of epitope some of which differ form the conventional antibodies. Other limitations of wherein constant heavy chain are from different specie of mammal was routine optimization and was well known in the art and therefore obvious variables when optimizing to use either a constant region of same specie or a

constant region of different species in view of Green. Further in view of the high level of skill in molecular biology techniques at the time of filing, one of the ordinary skills in the art would expect a reasonable expectation of success in modifying the transgene by substituting VHH coding sequence in the method disclosed by Surani et al for producing heterologous antibody of different isotype using the method disclosed by Loneberg in mouse such that functional CH1 domain in the constant heavy chain gene is not expressed. One of ordinary skill in art would have been motivated to combine the teaching of Surani et al, Loneberg, Nguyen et al and NCBI accession number because the method would have yielded a single heavy chain VHH antibody for therapeutic use.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claim 33 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Surani et al (US Patent no 5545807, dated 8/13/1996), Lonberg et al (US Patent no 5625126, dated 4/29/1997), Nguyen et al (Molecular Immunology, 1999, 515-524, IDS) and NCBI accession no. (AF305944, dated 3/15/2001) as applied to claims 2, 7, 10-11, 39, 41 and 43 above, and further in view of O'Keefe et al (US 20020147312, dated 10/10/2002, effective filing date 2/2/2001).

The reference of Surani et al, Lonberg et al (US Patent no 5625126, dated 4/29/1997), Nguyen et al and NCBI accession no have been described before and relied in same mummer here. While combination of references teach a method for producing a single heavy chain antibody in a transgenic mouse comprising expressing a heterologous VHH heavy chain locus, but differ from claimed invention by not disclosing entire VHH coding single chain locus is of camelid origin.

However, such was known in prior art. For instance, O'Keefe et al teaches constant region of antibody can be replaced with another constant region using techniques known in art. Specifically, O'Keefe et al disclose that constant region of other species including rodent, camel and rabbit are known in art and routinely used to produce antibody (see page 11, para. 18 and reference cited therein).

It would have been obvious for one of ordinary skill in the art at the time of invention to combine the respective teachings to modify the method by using substituting constant chain regions from one species disclosed by Surani et al/ Lonberg et al with another from camel using r known method to produce single heavy chain antibody. A person of skill in the art would have been motivated to substitute constant chain of one specie with another such as camel, as a matter of design choice, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since O'Keefe et al had already disclosed that constant region of different species including rodent, camel and rabbit were routinely used to produce antibody, while Surani et al, Loneberg and Nguyen taught method of generating single heavy chain antibody. Thus, it would have only required routine experimentation for one of

ordinary skill in the art to isolate antibody in the method disclosed by Surani et al, Loneberg and Nguyen using the constant region from camel origin as required by the instant claims.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claim 44 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Surani et al (US Patent no 5545807, dated 8/13/1996), Lonberg et al (US Patent no 5625126, dated 4/29/1997, art of record), Nguyen et al (Molecular Immunology, 1999, 515-524, IDS) and NCBI accession no. (AF305944, dated 3/15/2001).as applied to claims 1, 7, 10-11, 39, 41, 43 above, and further in view of Davies et al (Protein Eng. 1996, 531-537, IDS).

The reference of Surani et al, Loneberg, Nguyen et al and NCBI accession no have been described before and relied in same mummer here. While combination of references teach a method for producing a single heavy chain antibody in a transgenic mouse comprising expressing a heterologous VHH heavy chain locus, but differ from claimed invention by not disclosing isolating various variable fragments using phage display.

However, such was known in prior art. For instance, Davies teaches a method to isolate antigen specific VH domain using phage display (see page 532, col. 1, para. 2).

It would have been obvious for one of ordinary skill in the art at the time of invention to combine the respective teachings to modify the method of Surani et al. Loneberg and Nguyen et al with another known method to isolate antigen specific VH domain using phage display as disclosed by Davies et al. A person of skill in the art would have been motivated to isolate variable region fragment using phage display disclosed by Davies, as a matter of design choice, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since Davies et al had already disclosed that phage display could be used to isolate variable region fragment, while Surani et al and Nguyen taught method of generating single heavy chain antibody. Thus, it would have only required routine experimentation for one of ordinary skill in the art to isolate antibody in the method disclosed by Surani et al and Nguyen using the known phage display methods such as required by the instant claims.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Response to arguments

Applicants' arguments filed October 16, 2009 have been fully considered but are found not persuasive. Applicants disagree with the rejection and argue that the rejection is clear use of hindsight. Applicants also assert that the motivation provided in the office action is an example

of ex post reasoning. Applicants also argue that there was no reasonable expectation of success because at the time of filing it was not known whether camelid heavy chain only antibodies are generated in the same B-cells as regular tetrameric camelid antibodies comprising heavy and light chain or whether camelid heavy chain antibodies are produced in a specialized class of camelid B-cell. Applicants cite post filing art of Zou (2005, J.Immunol. 175, 3769-3779) and Nguyen (Immunology, 2003, 109:93-101, IDS) in support of these assertions (see page 9 and 10 of the arguments).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the instant case, base claims require immunizing a nonhuman mammal comprising expressing a heterologous VHH heavy chain locus in that mammal specifically in B-cell, wherein VHH heavy chain locus is integrated in the genome of said mammal. In this regard, Surani et al teach a method to produce an antibody in a transgenic mouse comprising a heterologous chimeric construct that generates antibody specifically in B cells of said mouse in response to antigen challenge, wherein the hybrid unrearranged immunoglobulin heavy chain gene comprising a mouse VH gene segment, a human VH gene segment, human D gene segments, human J gene segments, and a gene segment encoding a human mu constant effector region (see col. 3, lime 7-16 and col. 4, line 9-47). It is noted that Surani et al also teach that the vector also contains the necessary IgH enhancer required for B-cell specific expression (see col. 14, line 37). To the extent Surani et al. describe a method that uses a transgenic non-human mammals which co-express functional immunoglobulin transgenes which respond in a B-cell specific manner to antigen challenge and also teach the assembly of heavy chain loci comprising V, D and J genes, and constant regions, the rejection is applicable to the instant case. Applicants' selective reading of Surani et al. ignores the teachings of Lonberg et al, Nguyen and NCBI

accession no. There is no requirement for Surani et al. to teach that which is clearly taught by Lonberg et al, Nguyen and NCBI accession number.

A person of skill in the art based upon the need to enlarge the primary Ag-binding repertoire of the HCAb using a VHH coding sequence taught by Nguyen et al/NCBI accession no and in view of detailed guidance provided in the Loneberg and Surani et al specification of administering chimeric construct, cloning methodology and method for gene for generating heterologous antibody in a mouse, it would have been *prima facie* obvious to combine the teaching to modify the method of Surani et al by substituting the VH gene segment with functional equivalent a VHH exon comprising naturally occurring VHH coding sequence disclosed by NCBI accession, as a matter of design choice, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One of ordinary skill in the art would be motivated to do so as single chain heavy antibody recognizes broad range of epitope some of which differ form the conventional antibodies. Applicants should further note that prior art also taught the switch region from different isotype that could be operatively linked to a particular constant region (see Loneberg, supra), and it would have been obvious for one of ordinary skill in the art to use either a switch region of same isotype or a switch region of different isotype as a matter of design choice to promote class switch to any particular constant region gene.

With respect to applicants' argument of predictability, it should be noted that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988). Nguyen et al had already described that heavy-chain antibodies (HCAbs) lack the segments of first domain of the constant region (CH1), thus one of ordinary skill would be motivated to splice CH1 domain such that constant heavy chain gene when expressed does not express a functional CH1 domain to produce only single heavy chain antibody devoid of light chains. Applicants should note that the teaching of Surani et al, Loneberg and Nguyen et al was not based on the absence of a functional CH1, but on the prior art need to produce recombinant single chain heavy antibody.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., camelid heavy chain antibodies using camelid VHH) are not recited in the rejected claims 1, 10, 11, 33, 39, 41, 43-44. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants argue that it was not known whether camelid heavy chain only antibodies are generated in the same B-cells as regular tetrameric camelid antibodies or in a specialized class of camelid B-cell. In response, it should be noted that applicants' have previously argued that the assembly of complex heavy chain immunoglobulin loci as functional transgenes was well established in the art prior to the filing date (See applicants' argument filed 9/29/2008, page 18 and reference of Xu et al). In this context, Examiner has cited reference of Xu et al (Immunity 2000 13, 37-45, without relying for rejection) as pertinent art showing that the presence of one single V gene is sufficient to obtain functional antibody. Thus, one of ordinary skill in the art at the time of the invention was aware of assembly of complex heavy chain immunoglobulin loci as functional transgene. In view of the high level of skill in molecular biology techniques at the time of filing, one of the ordinary skills in the art would expect a reasonable expectation of success in modifying the method disclosed by Surani et al by substituting VH coding sequence with VHH for producing heterologous antibody in mouse such that functional CH1 domain in the constant heavy chain gene is not expressed. In the instant case, "if applicant is attempting to assert unexpected results in the formation of camelid heavy chain only antibodies, then such needs to be asserted by one of knowledge in the form of a declaration under 37 § CFR 1.132.). An affidavit or declaration under **37 CFR 1.132** must compare the claimed subject matter with the closest prior art to be effective to rebut a *prima facie* case of obviousness. *In re Burckel*, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979)

With respect to claims 33 and 44, applicant's arguments all rely on the arguments that have been previously discussed (see above). In absence of any new arguments, the rejection to claims 33 and 44 are maintained for the reasons of record and discussed above.

Conclusion

No claims allowed

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Xu et al (Immunity 2000 13, 37-45) show that the presence of one single V gene is sufficient to obtain function antibody.

Green et al (20030093820, dated 11/30/2001, art of record)

Riechmann et al (J Immunol Methods. 1999; 231(1-2): 25-38, art of record).

Imam et al (2000) *Nucleic Acids Res* 15, E65.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/
Primary Examiner, Art Unit 1632

Anoop Singh
AU 1632